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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,497	02/17/2000	DAVID J. FITZGERALD	015280-317100US	4036

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	21

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/381,497	FITZGERALD	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-14,16,17,22-27 and 29-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-14,16,17,22-27 and 29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The request filed on 3/7/02 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/381,497 is acceptable and a RCE has been established. Claims 1-5, 7-14, 16-17, 22-27, 29-32 are pending and are currently under prosecution. An action on the RCE follows.

Claims 1, 5, 8, 9, 11, 12, 16, and 27 have been amended.

Claims 6, 15, 28, and 40-49 have been canceled.

Claims 1-5, 7-14, 16-17, 22-27, 29-32, 22-32 are under examination.

2. The text of those sections of title 35, USC Code not included on the Office Action can be found in a prior Office Action.

3. The following Office Action contains some NEW GROUNDS of rejection

Claim Objections

4. Claim 1 is objected to because of the following informalities: Claim 1 contains a typographical error in the term "ds(Fv)" in the last line of claim 1. The term should be "dsFv". Appropriate correction is required.

Specification

5. The disclosure is objected to because of the following informalities: The first line of the specification should be updated to indicate this application claims benefit to provisional application 60/041437, filed 3/19/1997.

Appropriate correction is required.

Rejections Withdrawn

6. The rejection of claims 1-5, 7-14, 16-17, 22-27, 29-32 , 22-32 under 35 U.S.C. 103(a) as being unpatentable over Ghetie et al (Cancer Res. 51:5876-5880, 1991) and further in view of Reiter et al (Biochemistry 33:5451-5459, 1994) and Kuan et al (Biochemistry 35:2872-2877, 1996, Abstract published 2/1/96) is withdrawn in view of the new rejection.

7. The rejection of claims 42-47 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

Response to Arguments

8. The rejection of claims 1-4, 7, 11, 22-26, 29-32 under 35 U.S.C. 112, first paragraph, is maintained and made again.

The response filed 3/7/02 has been carefully considured but is deemed not to be persuasive. The response states "it was well known in the art at the time the invention was made that epitopes could be mapped using a number of techniques including steric competition assays" (see page 6 of response). In response to this argument, claims 1, and 11 have been amended to recite "competes for binding to a same epitope as an RFB4 disulfide-stabilized Fv". The response argues that it was well known to determine epitopes, however, as evidenced from Greenspan et al cited in the previous Office

action, it is not that easy. The response does not address the art of Greenspan et al. In addition the claims also encompass an antibody that does not bind to the same epitope (if so determined) as the RFB4 dsFv antibody. The immunoconjugate only needs to compete for binding, which at high enough concentrations antibodies with very low affinity for CD22 would bind. In addition, competing for the same epitope does not necessarily mean binding to the same epitope. The antibody could bind to another epitope and mask the epitope bound by the RFB4 antibody. As stated in the previous Office Action the specification enables an immunoconjugate comprising a toxin of PE or PE38 or a detectable label peptide linked to a recombinant anti-CD22 antibody of RFB4 with a VL of SEQ ID NO:4 which contains a cysteine at amino acid position 100 and a VH of SEQ ID NO:2 with a cysteine at position 44, wherein the VH chain is covalently attached to the amino terminus of PE or PE38 and the VL and VH are linked through a liner peptide of SEQ ID NO:5 or through a cysteine-cysteine disulfide bond, and does not enable any other antibody that would compete for the same epitope (which is not defined in the specification) as that of RFB4.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

The following are some NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-5, 7-14, 16-17, 22-27, 29-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 11 have been amended to recite the limitation a recombinant immunoconjugate... and has 90% or greater of the binding affinity of the RFB4 ds(fV)". (this rejection is not based on the typographical error in the term "ds(fv)"). The limitation of an immunoconjigate which has 90% or greater of the binding affinity of the RFB4 dsFv is not apparently found at page 15, lines 10-14 as stated in the response filed 3/7/02 (see page 4 of response). At the cited page the specification is referring to a "RFB4 binding fragment" and no mention of an immunoconjugate is seen. The claims encompass an immunoconjugate with the recited % affinity and this limitation is not seen at the cited page in the specification. Applicant is required to provide specific support for the limitation in the specification as originally filed or remove the limitation from the claims.

Claim Rejections - 35 USC § 103

11. Claims 1-5, 7-14, 16-17, 22-27, 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghetie et al (Cancer Res. 51:5876-5880, 1991) and further in view of Shen et al (Int. J. Cancer 42:792-797, 1988) and Reiter et al (Biochemistry 33:5451-5459, 1994) and Kuan et al (Biochemistry 35:2872-2877, 1996, Abstract published 2/1/96) and Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989).

The claims recite an anti-CD22 antibody of RFB4 which competes for binding to the same epitope of RFB4 dsFv comprising a PE and a VH with a cysteine at position 44 and a VL with a cysteine at position 100 wherein the VH is SEQ ID NO:2 and the VL is SEQ ID NO:4, wherein the VH is bonded to the amino terminus of PE and the VH and VL are bonded through a linker of SEQ ID NO:5 or cysteine-cysteine disulfide bond, an expression cassette comprising such, a host cell, a method of inhibiting the growth of malignant B-cells in a rodent.

Ghetie et al teach the RFB4 anti-CD22 antibody conjugated to ricin A chain and inhibition of growth of B-cell lymphomas in mice. Ghetie et al does not teach the hybridoma for RFB4, an anti-CD22 antibody with a VH with a cysteine at position 44 or a VL with a cysteine at position 100 conjugated to a cytotoxic fragment of PE wherein the VH is linked to the PE at the amino terminus, and the VH and VL are linked through a peptide linker that has SEQ ID NO:5 or a disulfide bond, or an expression cassette comprising such or a method of inhibiting the growth of malignant B-cells with a anti-CD22 antibody PE conjugate. These deficiencies are made up for in the teachings of Kuan et al, Reiter et al, Shen et al, and Orandi et al.

Reiter et al teach recombinant immunotoxins comprising disulfide stabilization with a cysteine at position 44 in the VH and a cysteine at position 100 in the VL. The antibody is conjugated to a toxin of PE38. Reiter et al also teach the VH is linked to the amino terminus of PE38 (see Figure 2). Reiter et al teach a general method for producing disulfide stabilized immunotoxins (see page 5453, Results).

Kuan et al teach a disulfide stabilized Fv directed to a cancer antigen. Kuan et al teach the VH is linked to the amino terminus of PE38 and the VH and VL are linked through a sequence that has SEQ ID NO:5 and the VH and VL are linked through a disulfide bond and expression cassettes and host cells comprising such.

Shen et al teach the hybridoma which produces the RFB4 antibody (see Antibodies under Material and Methods on page 792)

Orlandi et al teach a general method for obtaining the VH and the VL genes and the amino acid sequence of an antibody by PCR from the hybridoma cell.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody RFB4 and obtain the DNA and protein sequence of the VH and the VL from the RFB4 hybridoma as taught by Shen et al by the method of Orlandi et al and use the method of inhibiting malignant B-cells as taught by Ghetie et al and use the method of Reiter et al and Kuan et al to produce a disulfide stabilized anti-CD22 antibody conjugate.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody RFB4 and obtain the DNA and protein sequence of the VH and the VL from the RFB4 hybridoma as taught by

Shen et al by the method of Orlandi et al and the method of inhibiting malignant B-cells as taught by Ghetie et al and use the method of Reiter et al and Kuan et al to produce a disulfide stabilized anti-CD22 antibody conjugate because Ghetie et al teach that the RFB4 conjugates inhibited protein synthesis and when administered to mice with tumors, extended the mean survival time (see abstract). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody RFB4 and obtain the DNA and protein sequence of the VH and the VL from the RFB4 hybridoma as taught by Shen et al by the method of Orlandi et al and the method of inhibiting malignant B-cells as taught by Ghetie et al and use the method of Reiter et al and Kuan et al to produce a disulfide stabilized anti-CD22 antibody conjugate because Reiter et al teach a general method of stabilizing Fv's with insertion of cysteine residues in the conserved framework residues (see page 5453, Results) and "Neither molecular modeling nor knowledge of the structures of these Fv's was necessary to identify these positions" (see page 5453) and "disulfide-stabilized Fv's could be used not only to generate immunotoxins but also for all of the diagnostic and therapeutic uses proposed for single-chain antibodies or antigen binding proteins" (see page 5458). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody RFB4 and obtain the DNA and protein sequence of the VH and the VL from the RFB4 hybridoma as taught by Shen et al by the method of Orlandi et al and the method of inhibiting malignant B-cells as taught by Ghetie et al and use the method of Reiter et al and Kuan et al to produce a disulfide stabilized anti-CD22 antibody conjugate because Kuan et al

teach immunotoxins comprising a disulfide stabilized VH and VL wherein the VH is linked to the amino terminus of the PE38 and "We have compared the stability of three different single-chain and dsFv inmmunotoxins, and in all three cases the dsFv immunotoxins were more stable (see page 2872). Moreover, it would have been obvious to one of skilled in the art at the time the claimed invention was made to use a linker which has SEQ ID NO:5 to link the VH and the VL domains as was commonly performed. Also it would be obvious that the dsFv immunoconjugate using the antibody of Gettie would compete for binding to the same epitope as dsFv RFB4 because Ghetie et al's antibody is RBF4.

Although the references do not teach the amino acid sequences of SEQ ID NO:2 and 4 for the VH and VL of the anti-CD22 RFB4 antibody, it is the examiners position that the antibody of Ghetie et al which is produced by the hybridoma of Shen et al would have the sequence of the VH of SEQ ID NO:2 and a VL of SEQ ID NO:4. As taught by Orlandi et al it was routine to obtain the VH and the VL genes from PCR primers from the hybridoma of an antibody and "our primers might amplify most immunoglobulin mRNA of the mouse repertoire" (see page 3836, right column). As taught by Ghetie the RFB4 antibody is a mouse IgG1 (see page 5876, right column) and as taught by Shen is produced by a hybridoma cell. One of ordinary skill in the art would reasonably conclude that Ghetie et al's antibody also possesses the same VH and VL, therefore, it appears that Ghetie et al's would have the same VH and VL sequences of SEQ ID NO:2 and 4. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody with the antibody of Ghetie et al, the

burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The response filed 3/7/02 has been carefully considured but is deemed not to be persuasive. The response states "the Federal circuit has held that a nucleic acid sequence is not obvious over general methods of isolated cDNA or DNA molecules" (see pages 4-5 of response. In response to this argument, while the statement may be true for a general nucleic acid sequence, as cited in Orlandi et al above because of the homology in the VH and VL genes primers cam be made and were made to PCR out the VH and VL genes from mouse hybridoma cells. Thus, while cloning of a general gene may not be obvious, cloning of antibody VH and VL genes from hybridoma cells were routine at the time of applicants claimed invention. The response further states "The art does not predict which dsFv immunoconjugates would have these characteristics" as claimed and cites Reiter et al for teaching "the B3 and B1 antibody conjugates exhibited very poor binding properties relative to the native IgG, in contrast to dsFvRFB4" (see page 5 of response). In response to these arguments, Table 3 of Reiter et al is directed to comparison of dsFv-PE38 conjugates to IgG, scFv-PE38 or Fab fragments. The reference does not compare the dsFv to the dsFv-PE38

immunoconjugate. The claims recite an immunoconjugate which has 90% or better binding affinity of the dsFv. In addition, Reiter et al (Biochemistry 33:5451-59, 1994) teach the dsFv-immunotoxins have equal or improved activity (see abstract) and thus one skill in the art would expect the immunoconjugate to be as active or better than the dsFv alone. Moreover, Reiter et al (Nature Biotech) teach 4 out of 8 dsFv-immunotoxins had improved binding affinity (see page 1243, left column).

Conclusions

12. No Claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the

Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879